REMARKS/ARGUMENTS

Claims 2, 5-6, 8, 9, 11, 12, 14-38 and 53-59 are currently pending in the subject application. Applicants have added claims 60-65. Support for the new claims may be found, inter alia, in the originally-filed specification as follows: claims 60 and 61, on page 3, lines 15-17; claim 62, on page 4, lines 25-26 and lines 16-17; claim 63, on page 4, lines 21-22; claim 64, page 12, lines 5-6; and claim 65, on page 15, lines 5-7. Claims 6, 8, 9, 11, 12, 14-38 and 59 have been amended to clarify the claimed subject matter and/or to correct typographical errors. All new claims read on the elected species. Applicants submit that this amendment does not involve any issue of new matter. Applicants respectfully request entry of this amendment such that claims 2, 5-6, 8, 9, 11, 12, 14-38 and 53-65 will be pending.

Claim Rejections - 35 U.S.C. §103

The Examiner maintains the rejection of claims 2, 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35-38, 53, 56 and 57 under 35 U.S.C. 103(a) as being allegedly unpatentable over Kelly (U) in view of Kubbersampath (AG) and Lefer(V). The Examiner further rejects claims 2, 15-20, 53, 54, 55, 58 and 59 and as being unpatentable over Kelly (U) in view of Kubbersampath (AG) and Lefer(V), and further in view of Anderson(U) and Brady (W).

The Examiner maintains the obviousness rejection, alleging that Applicants have not set forth sufficient evidence to *rebut* the presumption of prima facie obviousness. The Examiner, however, has failed to satisfy his initial burden of establishing a prima facie case of obviousness. Applicants have presented evidence that at least one of the three elements of the prima facie case is lacking: a reasonable expectation of success. Rather than *rebutting* a prima facie case of obviousness, applicants show here, and have shown in previous submissions, that the Examiner has failed to meet his initial burden under MPEP 2142 of establishing the prima facie case. In the office action, the Examiner seeks to prematurely shift the burden of proof to Applicants, when the Examiner's own initial burden of proof has not yet been satisfied. Specifically, the Examiner is requiring applicants to prove that OP-1 would not be expected to exhibit the harmful renal effects of other anti-inflammatory agents, when it is the Examiner who bears the initial burden of showing why OP-1 should be considered as the exception amongst anti-inflammatory agents.

I. Reasonable Expectation of Success is Lacking

MPEP 706.02(j) sets forth three basic criteria needed to establish a *prima facie* case of obviousness: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

In previous submissions, applicants have set forth ample evidence that Transforming Growth Factor Beta 1(TGFβ1), Cyclosporin A (CsA) and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were known at the time the subject application was filed to be both (i) anti-inflammatory agents which inhibit ICAM adhesiveness, and (ii) *detrimental* to renal function. One skilled in the art, then, would not have had any reasonable expectation of success for improving renal function in a subject afflicted with acute renal failure (ARF) using the anti-inflammatory agent OP-1. Hence, the third requirement has not been met, and therefore a case of *prima facie* obviousness not made.

In response, the Examiner alleges that there is no evidence of record that OP-1 possesses any of the renal side effects of TGFβ1, CsA or NSAIDS. The Examiner claims that applicants have not met a burden of proof in providing a nexus between (i) anti-inflammatory agents inhibiting ICAM adhesiveness and (ii) anti-inflammatory agents being detrimental to acute renal function. But the burden is on the Examiner, not on applicants, to establish the third prong of the prima facie case of obviousness. It is the Examiner who must present evidence why one skilled on the art would have expected a fourth anti-inflammatory agent (OP-1) to be effective in treating acute renal failure when three others anti-inflammatory agents were known to *exacerbate* renal failure.

If at least three other classes of anti-inflammatory were known to have adverse effects on renal function, why would one skilled in the art have expected OP-1 as well as other morphogens to be the exception? Applicants respectfully submit that the Examiner has failed to provide a plausible rationale. The Examiner makes several allegations in the current Office Action and in prior office action; however none of these office actions explain why OP-1 (or any other morphogen) would be expected by the skilled artisan to be the exception amongst anti-inflammatory agents. The Examiner's allegations include the following:

(i) The Examiner alleges that despite the evidence showing the ineffectiveness of anti-inflammatories in treating ARF, one could not have known for sure whether OP-1 would fail in treating ARF until it was actually tested. But again, the standard is the expectation that something would work or fail, and not whether there was actual direct experimental evidence that it would fail.

(ii) The Examiner points to differences between OP-1 and TGFβ1 in bone formation to suggest that the two TGFβ-family members might have different biological properties in treating other organs. The question, however, is not whether the possibility exists, no matter how small, that two compounds can have different properties; the question is what properties one skilled in the art would have expected the morphogens to have. The Examiner fails to meet his burden of proof for showing why one skilled in the art would expect OP-1 to be the exceptional anti-inflammatory agent. He merely points out that OP-1 is a different compound than TGFβ1, CsA or an NSAID.

(iii) The Examiner presents an analogy, claiming that if 50% of women have brown hair, then brown hair cannot be said to be the cause of cancer. This analogy is unrelated to the issues set forth by applicants. The question that must be answered by the Examiner in attempting to establish a prima facie case of obviousness is this: if three anti-inflammatory agents are known to exacerbate renal function, why would one skilled in the art expect a fourth agent, which is selected solely based on its anti-inflammatory properties, to improve renal function during acute renal failure? In essence, why would one skilled in the art expect the fourth anti-inflammatory agent to be the exception? The anti-inflammatory properties of OP-1 are not a random property of the morphogen that can be ignored by the examiner when it is precisely those properties that the Examiner claims would draw one skilled in the art to select it as a therapeutic.

In summary, the Examiner has focused exclusively on OP-1's alleged anti-inflammatory property as the key attribute in making it a successful candidate for treating ARF. Applicants have proven that anti-inflammatory properties are not sufficient to treat ARF, and that in fact, anti-inflammatory agents have detrimental effects on renal function. While having the burden of proof, the Examiner has failed to set forth evidence as to why one skilled in the art would have made OP-1 the exception amongst anti-inflammatory agents. The burden is on the Examiner to provide such evidence, and he has failed to do so. Based on the failure to set forth a reasonable expectation of success, a case of *prima facie* obviousness has not been made in accordance with MPEP 706.02(j).

Applicants request reconsideration and withdrawal of this ground of rejection.

II. The Examiner has Failed to Examine the Elected Species *i.e.* Pre-renal Causes of ARF and Has Instead Examined Intrinsic Causes

In the Office Action of May 6, 2002, the Examiner requested a species election of causes of ARF for search purposes only, *i.e.* an election between pre-renal causes, post-renal causes and intrinsic renal causes of ARF. Applicants elected, for search purposes "pre-renal causes of acute renal failure" in the response filed on August 6, 2002. Dependent claim 20 recites several forms of pre-renal causes of ARF. Claims 21 and 22, currently withdrawn, recite forms of post-renal and intrinsic causes, respectively.

Even if the Examiner had made a case of *prima facie* obviousness, which he has not, based on the Examiner's arguments at most it would relate to using OP-1 to treat ARF caused by renal ischemia. Renal ischemia is not a pre-renal cause of ARF and thus not within the elected species.

The 103(a) rejection relies, in part, on two references, Kelly and Kubbersampath, that relate to ARF caused by damage to renal tissue ischemia or inflammation. Kelly induces renal ischemia in a mouse by clamping the renal arteries: "[u]sing a midline abdominal incision, renal arteries and veins were bilaterally occluded for 32 min with microaneurysm clamps, during which time the abdomen was closed. The time of ischemia was chosen to maximize reproducibility of renal functional impairment while minimizing animal mortality in these animals, who were not administered fluid intravenously" (see 3rd paragraph of the methods section). Similarly, as acknowledged by the Examiner on page 4, 1st paragraph in the Office Action of July 12, 2004, Kubbersampath relates to glomerulonephritis caused by unwanted inflammation and fibrosis.

Renal ischemia and glomerulonephritis are forms of *intrinsic* renal failure, not *pre-renal* causes. The second paragraph of the background of the invention in the originally-filed specification (page 1, lines 16-32) states that "intrinsic causes of acute renal failure include but are not limited to infectious diseases (*e.g.* various bacterial, viral or parasitic infections) inflammatory diseases (*e.g.* glomerulonephritis, systemic lupuserythromatosus, ischemia (*e.g.* renal artery occlusion), toxic syndromes..." (emphasis added). By contrast, "pre-renal causes...do not involve direct damage to the kidneys" (same paragraph).

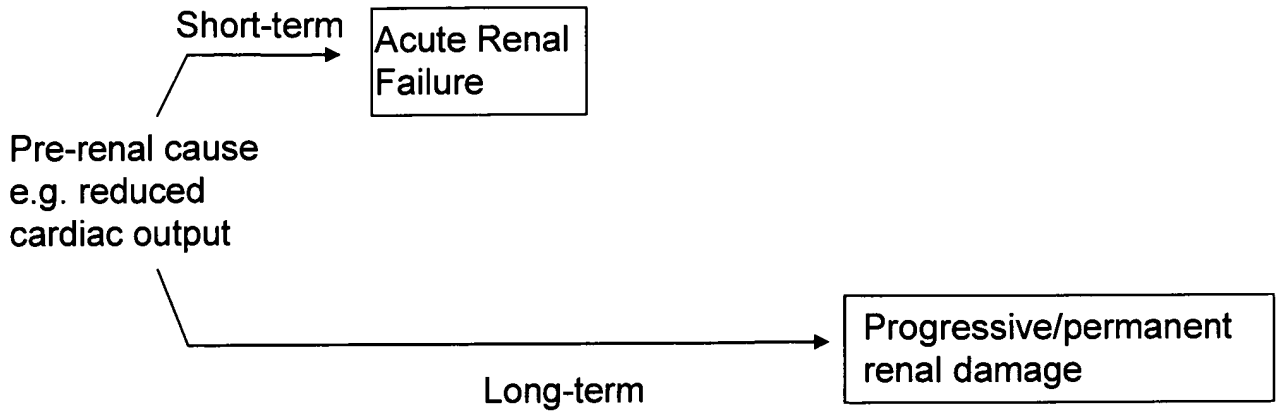
The classification of ischemia and glomerulonephritis in the specification as intrinsic causes of ARF is consistent with the art. U.S. Patent No. 5,576,287, granted November 19, 1996 states in column 1, lines 29-32 that "[r]enal ischemia is one of the most common intrinsic renal causes of ARF. In general, renal ischemia refers to localized tissue hypoxia within kidneys that results from the obstruction of the inflow of blood or low blood oxygen levels" (emphasis added). Similarly, the middle part of Table 236-1 on page 1266 of Harrison's Principles of Internal Medicine, 13th Edition, McGraw Hill Co., 1994, similarly teaches that renal artery/vein occlusion and glomerulonephritis are forms of intrinsic renal failure, and not forms of pre-renal ARF (See Exhibit A of November 15, 2005 Amendment). Intrinsic ARF is characterized by damage to the renal tissue, which may be caused by hypoperfusion (such as by clamping of renal arteries) or by toxin damage (see page 1267, column 1, last paragraph of Harrison's).

In contrast, page 1266, first full paragraph of Harrison's teaches that *pre-renal* ARF "is due to a functional response to renal hypoperfusion and is rapidly reversible upon restoration of renal blood flow and glomerular filtration pressure." This section of Harrison's also teaches that in *pre-renal* ARF, renal parenchymal tissue is *not* damaged.

The Examiner counters by focusing on page 1, lines 21-25 of the specification. The Examiner may have inadvertently distorted the import of this section of the specification by redacting it as follows: "Pre-renal causes ... may lead to significant permanent and/or progressive damage to renal tissue." However, the full sentence in the specification actually reads as follows:

> Pre-renal causes (e.g. decreased cardiac output, hypovolemia, altered vascular resistance) and post-renal causes (e.g. obstructions or constrictions of the ureters, bladders or urethra) do not involve direct damage to the kidneys but, by affecting the blood flow to the kidneys or the flow of urine from the kidneys, may lead to significant permanent and/or progressive damage to renal tissues."

Accordingly, some pre-renal causes of ARF have two effects: a short-term acute renal failure and a progressive and permanent damage to the kidneys. This is diagrammed as follows:



Therefore, even if a valid prima facie case of obviousness had been made for treating long-term permanent renal damage arising from a pre-renal cause, which it has not, a prima facie case of obviousness was not made for treating the acute renal failure arising from pre-renal causes. The pending claims recite improving a standard of renal function in a mammal afflicted with acute renal failure, and not for treating a mammal with renal damaged caused by continued pre-renal causes of ARF. Since the references fail to teach that OP-1 or other morphogens can be used to treat the acute renal failure caused by pre-renal output, as recited in the pending claims, the references fail to teach all the elements of the claimed invention. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Identification of Grounds of Rejection for Each Claim

In preparation for a possible appeal, applicants respectfully request that the Examiner identify where the elements of each of the rejected claims, both dependent and independent claims, are allegedly taught by the references should the Examiner maintain the rejection.

MPEP 706.07 requires that all outstanding grounds of rejection be clearly developed by the Examiner so that applicants may readily judge the advisability of appeal: "In making the final rejection, all outstanding grounds of rejection of record should be carefully reviewed, and any such grounds relied on in the final rejection should be reiterated. They must also be clearly developed to such an extent that applicant may readily judge the advisability of an appeal unless a single previous Office Action contains a complete statement supporting the rejection. (Emphasis added)." Applicants submit that no previous office action provides a complete statement of the supporting rejection.

Furthermore, although applicants added two new claims in the previous amendment, claims 58 and 59, the Office Action failed to explain how all the elements in these claims are allegedly taught by the references. In addition, applicants added new claims 60-65. Applicants respectfully request that, should these new claims be rejected that the Office Action, the Office Action explain how the elements of each of these claims is allegedly taught by the art so that applicants may readily judge the advisability of appeal.

Conclusions

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicant believes no fee is due with this response other than the fees itemized in the accompanying fee transmittal form. If an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P01-514 from which the undersigned is authorized to draw.

Dated: June 29, 2006

Respectfully submitted,

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